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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/611,949	07/06/2000	David M. Margolis	968173.00001	6524

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EXAMINER	
GUZO, DAVID	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/611,949	MARGOLIS ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006 and 10 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

35 USC 112, 1st Paragraph Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons pf record in the previous Office Action (mailed 2/16/06) and for reasons outlined below.

Applicants traverse this rejection by supplying a 37 CFR 1.132 Declaration from inventor David M. Margolis (hereafter the Margolis Declaration). Applicants argue that the data presented in the Margolis Declaration (also presented in the Lehman et al. paper (The Lancet, August 13, 2005, Vol. 366, pp. 549-555) demonstrate enablement for the claimed invention. The Margolis Declaration (and attached Lehman et al. paper) recite a proof-of-concept study in four volunteers infected with HW and on highly-active antiretroviral therapy (HAART). After intensifying the effect of HAART with subcutaneous enfuvirtide (90 μg twice daily for 4-6 weeks to prevent the spread of HIV), valproic acid 500-750 mg was administered orally twice daily to their treatment regimen for 3 months. Latent infection of resting CD4+ T cells was quantified before and after

augmented treatment by limiting-dilution culture of resting CD4+ T cells after *ex-vivo* activation. Results indicate that the frequency of resting CD4+ T cell infection was stable before addition of enfuvirtide and valproic acid, but declined thereafter and this decline was significant in three of the four patients (mean reduction 75%, range 68% to >84%). Declarant indicates that these results demonstrate that combination therapy with an HDAC inhibitor and HAART safely accelerates clearance of HIV from resting CD4+ T cells *in vivo*.

Applicants' arguments and the Declaration under 37 CFR 1.132 filed 7/17/06 are insufficient to overcome the rejection of claim 11 based upon 35 USC 112, 1st paragraph (enablement) as set forth in the last Office action because: The experimentation outlined in the Declaration (and paper) is not supported by the instant application, as filed. First, the instant application does not disclose administration of valproic acid (VPA) as an inhibitor of HDAC1. Second, the instant application does not disclose administration of enfuvirtide as an anti-retroviral drug. Third, the instant application does not recite **augmenting** a highly active antiretroviral therapy (HAART) by addition of enfuvirtide at the recited levels of 90 μg administered subcutaneously twice daily for 4-6 weeks prior to administration of VPA. Fourth, the instant application does not teach or suggest the dosages of VPA administered to the patients. Fifth, the instant application does not teach or suggest the combination of VPA and enfuvirtide. Sixth, the instant application does not recite HAART or augmenting HAART with any additional anti-retroviral drugs prior to administering VPA or any other HDAC1 inhibitor. For declarant's data to be effective in overcoming an enablement rejection under 35

USC 112, 1st paragraph, the data in the Declaration must be supported by the application as filed. Clearly, the experimental protocols and drugs recited by declarant are not supported by the instant application and appear to be based upon discoveries made after the effective filing date of the instant application. Therefore, the data presented in said declaration is not sufficient to overcome the instant rejection.

The following additional points are noted. The basis of applicants' invention appears to be that inhibitors of HDAC1 in combination with anti-retroviral drugs can reduce the pool of $CD4^+$ T-cells which are latently infected with HIV-1, thereby reducing or eliminating the so-called viral reservoir. However, because applicants administered two new drugs (enfuvirtide and VPA), it is unclear what contribution each drug made to the observed results. The lack of controls in the study also makes interpreting the results difficult. As noted by Smith (Retrovirology, 2005, Vol. 2, p.56, cited by applicants), in an analysis of declarant's results, presented in the Lehman et al. paper), it is unclear how HIV transcription is up-regulated in resting $CD4^+$ cells:

> Of considerable interest is the potential mechanism by which VPA reduces the frequency of latently infected, resting $CD4^+$ T-cells. Presumably, through inhibition of HDAC, VPA allows initiation of viral transcription, which in turn leads to production of viral proteins and virions, and cell death due to virally induced cytotoxicity. **Paradoxically, VPA does not activate resting $CD4^+$ T-cells, thus making it unclear how HIV transcription is upregulated and viral promoter activity is increased** (emphasis added).

Given these considerations, it is unclear whether any HDAC1 inhibitor would have the same effects on HIV transcription in latently infected resting $CD4^+$ T-cells.

For the reasons of record and for reasons outlined above, the rejection is maintained.

Sequence Listing

The Sequence Listing filed 7/17/06 has been entered.

Miscellaneous

The amendment filed is technically not in compliance with 37 CFR 1.121 in that in line 5, the word "viral" is underlined and crossed through. Applicants are encouraged with comply with the rules for making amendments in any future submissions.

No Claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, PhD, whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, PhD, can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
December 2, 2006

DAVID GUZO
PRIMARY EXAMINER